## REMARKS

***Status of the claims***

Claims 1, 2, 4-18 and 20-35 are pending in this application.

***Withdrawn rejections***

The Final Office Action dated October 28, 2008 (hereinafter referred to as the "Office Action") withdrew all objections to the specification and claims. Applicants gratefully acknowledge the withdrawal of these objections.

The Office Action also withdrew rejection of claims 1-2, 4-6, 18 and 19-22 under 35 U.S.C. §101, the rejection of claim 7 under 35 U.S.C. §112, second paragraph, and the rejection of claims 1-2, 4-6, 18 and 19-22 under 35 U.S.C. §102(b) as being anticipated by Shenoy et al. Applicants gratefully acknowledge the withdrawal of all of these rejections.

***Claim Rejection under 35 USC §112, 1st paragraph***

Claims 1, 2, 4-7, 18 and 20-22 are rejected under 35 USC §112, 1st paragraph, because the specification allegedly does not reasonably provide enablement for an arrestin chimera comprising an arrestin or a fragment of arrestin and a ubiquitin moiety or a fragment of ubiquitin, wherein the arrestin chimera has an increased affinity for a GPCR, as compared to the affinity of a wild-type arrestin, and wherein increased affinity means that the arrestin chimera remains associated with the GPCR and traffics with the GPCR into endosomes, and wherein the arrestin chimera does not dissociate at or near the plasma membrane. Applicants respectfully disagree.

As will be appreciated, the test of enablement is whether one reasonably skilled in the art could make or use the invention as claimed from the disclosure in the patent coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). *See* also MPEP §2164.01. One way to determine if undue experimentation is required is to utilize the *Wands* factors: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." All of the factors need not be reviewed when

determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991).

As the Office Action notes on page 3, the present specification is enabling for an arrestin chimera comprising a naturally occurring beta-arrestin-2 and a naturally occurring ubiquitin moiety (including an arrestin chimera comprising SEQ ID NO: 2). The Office Action goes on to assert that undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope, because "the claims encompass an essentially unlimited genus of chimeras of arrestin and ubiquitin variants that must be made and tested to determine whether or not they meet the functional limitations recited in the claims." *see Office Action, page 9.* Applicants respectfully submit that since the specification is enabling for an arrestin chimera comprising a naturally occurring beta-arrestin-2 and a naturally occurring ubiquitin moiety, then variations of such a chimera are also enabled by the disclosure of the present specification coupled with information known in the art.

Applicants respectfully submit that one of skill in the art would be able to use standard methods known in the art to extrapolate from the assays described in the present specification to determine whether an arrestin chimera is within the scope of the present claims. Arrestin chimeras are described throughout the specification, and multiple working examples describe assays utilizing such chimeras. For example, pages 29-34 provide several examples of assaying GPCR activity with modified arrestins, including arrestin chimeras according to the presently claimed invention. Pages 38-43 of the present specification provide further details on methods of detecting interactions between GPCR and arrestin chimeras of the invention, and pages 43-49 provide even more details on assaying GPCRs. The present specification also cites multiple references that further describe protocols and assays known in the art that could be used to determine whether a particular arrestin chimera falls within the scope of the present claims.

In discussing the arrestin chimeras represented by SEQ ID NOs: 4 and 6, the Office Action states that the "skilled artisan could not predict whether permanently monoubiquinated arrestin would have less, equal or greater affinity than transiently polyubquinated arrestin". Applicants respectfully submit that the test for enablement is not whether a skilled artisan would be able to predict whether a particular arrestin chimera would have equal or greater affinity for GPCR absent any experimental testing. The test is whether determining if a particular chimera falls within the scope of the claims requires "undue experimentation". Applicants further submit that unpredictability of whether a particular configuration of arrestin and ubiquitin displays the functional elements recited in claim 1 is balanced by the ease and routine nature of assays to detect those functional elements. The present application provides ample disclosure on the types of assays that can be used to detect those functional elements, and this disclosure, combined with what is known to one

of skill in the art, is ample for enabling the full scope of the present claims. For example, in paragraphs [0123] – [0127], the specification generally describes several different examples of assays that are known in the art that could be used to determine the affinity between a GPCR and a particular arrestin chimera. Paragraphs [0185] – [0192] provide further details of such assays by describing the different ways that GPCR or its binding partners can be labeled for use in assays of affinity. In addition, pages 51-60 provide working examples of several different assays of the interaction between GPCR and arrestin. Although not every possible arrestin chimera encompassed by the present claims is described in these working examples, Applicants respectfully submit that such description is not a requirement for enablement. One of skill in the art could use the assays described in the present specification to test any chimera encompassed by the claims without undue experimentation.

The courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. For example, see MPEP §2164.01.[1] As the *Wands* court explained:

> [A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.[2]

Practitioners in the chemical and molecular biology arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue. Based on the description of the assays provided in the present specification, one of skill in the art could determine whether a particular chimera falls within the scope of the presently claimed invention through routine experimentation that is empirical in nature, typically employing nothing more than performing the same assay disclosed in the specification on a variety of variants of the disclosed chimeras made by routine recombinant DNA techniques. Since these experiments are empirical in nature, no undue experimentation is required. In other words, the only experimentation that may be required to enable the claimed invention are those experiments to determine the presence of a certain activity, and since this only requires a routine assay on variants to determine whether they possess that activity, no undue experimentation is necessary.

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[1] See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).
[2] *In re Wands* 8 USPQ 2d at 1404.

The Office Action repeatedly asserts that "the essentially limitless size of the genus to be tested" and the "lack of predictability" of mutations that will impact the functionality of the chimera renders the experimentation undue. Applicants again submit that the means for practicing the invention as claimed, particularly assays for detecting the affinity of an arrestin chimera for GPCR are routine and well-established in the art. Since one of skill in the art would be able to, as a routine matter, determine whether an arrestin chimera has an increased affinity of a GPCR, and whether such a chimera remains associated with the GPCR and traffics with the GPCR in to endosomes, the level of experimentation required would not be considered undue. For example, on pages 54- 56, the present specification provides several working examples of assays for determining whether an arrestin chimera remains associated with the GPCR (which in these examples is the β2AR GPCR) and traffics with the GPCR into endosomes (for example, see paragraphs [0210] and [0214] as well as figures 7A and 4B). Under MPEP § 2164.02 the consideration is whether one skilled in the art would be expected to be able to extrapolate the provided examples across the entire scope of the claim. To determine whether any other chimera shows similar functional properties as the chimera described in the working examples of the present specification would require only routine experimentation by one of skill in the art. Even if a large number of variants are encompassed by the present claims, the number of possible variants alone can not be used to support a rejection for enablement. Compliance with the enablement requirement under Title 35 U.S.C. §112, first paragraph does not require or mandate that a specific example be disclosed. The specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice the invention without undue experimentation.[3] Furthermore, "[n]othing more than objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples."[4] Since the present application does contain working examples demonstrating exemplary methods of evaluating the affinity of a chimera for a GPCR, the present application does provide a person skilled in the art, through the specification as well as the working examples, sufficient enablement for the subject invention.

With respect to the assertion that the lack of predictability for which mutations in the arrestin and/or ubiquitin will impact the functionality of the chimera renders the amount of experimentation required by the present claims undue, Applicants respectfully submit that, as provided by MPEP §2164.03, "The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification...even in

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[3] *In re Borkowski*, 164 USPQ at 645.
[4] *In re Robins* 166 USPQ 552 at 555 (CCPA 1970).

unpredictable arts, a disclosure of every operable species is not required." Applicants submit that, given the state of the art, the specification provides sufficient detail to allow one of skill in the art to "extrapolate the disclosed or known results to the claimed invention." Thus, to the extent that practice of the invention is not predictable, one of skill in the art, armed with the teachings provided in the specification, can utilize predictable and routine methods to optimize reaction conditions and to assay whether the reaction has been successful.

In sum, the Applicants stress that the level of unpredictability in the field does not rise to the level of requiring undue experimentation by one of skill in the art, because the unpredictability of whether a particular chimera has increased affinity for GPCR according to claim 1 is balanced by the ease and routine nature of assays to detect that a transfer has taken place. Thus, one of skill could practice the full scope of the claimed invention without undue experimentation. Applicants respectfully request that this rejection be withdrawn.

## CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and early notification to that effect is respectfully requested. If the Examiner feels there are further unresolved issues, the Examiner is respectfully requested to phone the undersigned at (415) 442-1266 (direct line).

Respectfully submitted,
MORGAN, LEWIS & BOCKIUS LLP

Dated: January 28, 2009 By: _____
Gargi Talukder, Reg. No. 61,368 *for*
David J. Brezner, Reg. No. 24,774

Customer Number: 67374
Morgan Lewis & Bockius LLP
One Market Street, Spear Street Tower
San Francisco, CA 94105
Telephone: (415) 442-1266
Facsimile: (415) 442-1001
gtalukder@morganlewis.com